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REVIEW

Neuroimaging studies of GABA in schizophrenia: a systematic review with meta-analysis

A Egerton¹, G Modinos¹, D Ferrera^{1,2} and P McGuire¹

Data from animal models and from postmortem studies suggest that schizophrenia is associated with brain GABAergic dysfunction. The extent to which this is reflected in data from *in vivo* studies of GABA function in schizophrenia is unclear. The Medline database was searched to identify articles published until 21 October 2016. The search terms included GABA, proton magnetic resonance spectroscopy (¹H-MRS), positron emission tomography (PET), single photon emission computed tomography (SPECT), schizophrenia and psychosis. Sixteen GABA ¹H-MRS studies (538 controls, 526 patients) and seven PET/SPECT studies of GABA_A/benzodiazepine receptor (GABA_A/BZR) availability (118 controls, 113 patients) were identified. Meta-analyses of ¹H-MRS GABA in the medial prefrontal cortex (mPFC), parietal/occipital cortex (POC) and striatum did not show significant group differences (mPFC: $g = -0.3$, 409 patients, 495 controls, 95% confidence interval (CI): -0.6 to 0.1 ; POC: $g = -0.3$, 139 patients, 111 controls, 95% CI: -0.9 to 0.3 ; striatum: $g = -0.004$, 123 patients, 95 controls, 95% CI: -0.7 to 0.7). Heterogeneity across studies was high ($I^2 > 50\%$), and this was not explained by subsequent moderator or meta-regression analyses. There were insufficient PET/SPECT receptor availability studies for meta-analyses, but a systematic review did not suggest replicable group differences in regional GABA_A/BZR availability. The current literature does not reveal consistent alterations in *in vivo* GABA neuroimaging measures in schizophrenia, as might be hypothesized from animal models and postmortem data. The analysis highlights the need for further GABA neuroimaging studies with improved methodology and addressing potential sources of heterogeneity.

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INTRODUCTION

One of the most consistent findings from postmortem studies in schizophrenia is a reduction in the GABA-synthesizing enzyme, GAD67 mRNA and protein.^{1–3} Expression of GAD67 is activity regulated^{4,5} and GAD67 is responsible for over 90% of all (cytosolic) GABA production.⁶ In contrast to GAD67, inconsistent findings in schizophrenia are reported for the GAD65 isoform,^{7–10} which is involved in vesicular, synaptic GABA production during intense periods of neural activity.^{11,12} The potential effects of a reduction in GAD67 on cortical excitatory/inhibitory networks is a key component in some neurobiological models of schizophrenia.¹³ In particular, GABA dysfunction is thought to lead to the disinhibition of glutamatergic pyramidal neurons and a loss of synchronous cortical activity.^{14,15} Postmortem studies also suggest that schizophrenia is associated with dysfunctional GABA signalling at the postsynaptic receptor level. Receptor autoradiography using ³H-muscimol, an agonist at the GABA binding site on the GABA_A/benzodiazepine receptor (GABA_A/BZR) complex, has consistently shown an increase in binding density in the prefrontal, cingulate and temporal cortices and caudate nucleus.^{16–22} In contrast, density of binding to the BZ binding site of the GABA_A/BZR complex has been found unaltered, increased or decreased postmortem.^{22–27} Postmortem investigations of GABA_A α subunit expression have found reductions in $\alpha 1$ (refs 28,29) and increases in $\alpha 2$ (refs 29,30) expression in schizophrenia, but inconsistent results for the $\alpha 5$ subunit.^{29,31,32}

GABA function in schizophrenia can be assessed *in vivo* using neuroimaging techniques. Proton magnetic resonance spectroscopy (¹H-MRS) optimized for GABA detection can measure GABA concentrations within a voxel of interest. This approach measures total (intracellular and extracellular) GABA and macromolecules (denoted GABA+) across all tissue content in a relatively large voxel. An alternative neuroimaging approach is to use positron emission tomography (PET) or single photon emission computed tomography (SPECT) in conjunction with specific radiotracers that bind to GABA or BZ receptors.³³ However, all the PET/SPECT radiotracers currently available for human use bind to the BZ rather than to the GABA_A site of GABA_A/BZ receptors. The PET/SPECT radiotracers iomazenil and flumazenil have limited subunit selectivity, binding GABA_A/BZ receptors containing $\alpha 1$, $\alpha 2$, $\alpha 3$ and $\alpha 6$ subunits, whereas Ro15-4513 has more selectivity for $\alpha 1$ and $\alpha 5$.³⁴

Neuroimaging of GABA function is potentially important because several hypotheses around the role of GABA dysfunction in schizophrenia can only be tested *in vivo*. Evidence that GABA dysfunction has a role in the pathophysiology of schizophrenia has also led to interest in the therapeutic potential of pharmacological compounds that act on GABA function, and data from animal studies suggest that administration of benzodiazepines can prevent the development of neuro-anatomical and neurophysiological abnormalities associated with schizophrenia.^{35,36}

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Although there have been several neuroimaging studies of GABA in schizophrenia, the nature of GABAergic abnormalities in schizophrenia *in vivo* remains unclear. The present study aims to address this issue by conducting a systematic review and a meta-analysis of ^1H -MRS and PET/SPECT studies of GABA in schizophrenia. In our primary analyses as well as studies of patients with schizophrenia, we included studies of subjects at high clinical or genetic risk for the disorder, as GABAergic dysfunction may be a 'trait' characteristic, arising through the influences of genetic variation during development.³⁷ The potential influence of clinical subgroups,^{38,39} medication status,^{38,40} symptom severity,^{38,40,41} age^{42,43} and gender⁴⁴ were investigated using subsequent moderator analyses and meta-regression.

MATERIALS AND METHODS

Study selection

The meta-analysis and systematic review was performed in accordance with the guidelines of the PRISMA group.⁴⁵ The Medline electronic database was searched to identify journal articles published from 1 January 1950 until 21 October 2016, using the following MeSH and freeform search terms: ('GABA') AND ('MRS' OR 'spectroscopy' OR 'positron emission tomography' OR 'single photon emission tomography' OR 'single photon emission computed tomography' OR 'PET' OR 'SPET' OR 'SPECT') AND ('schizophrenia' OR 'psychosis' OR 'schizophreniform' OR 'psychosis risk'). Reference lists of the returned articles were hand searched for further relevant publications. Two authors independently performed the searches and identified articles for inclusion (AE and DF).

Inclusion required that articles were published in peer-reviewed journals in English or English translation. Inclusion also required that articles reported GABA measures *in vivo*, in a group with clinical diagnosis of schizophrenia, schizoaffective disorder or first episode psychosis, or a group at clinical or genetic risk for schizophrenia, compared with a healthy volunteer (control) group. ^1H -MRS studies were excluded if they reported the GABA signal only as the combined signal with glutamate (Glx). PET/SPECT studies were excluded if they investigated translocator protein, which mediates various mitochondrial functions and was previously described as the peripheral benzodiazepine receptor.⁴⁶ Where articles reported overlapping samples, only data from the article reporting the largest sample was included.

Outcome measures

The primary outcome measure was the control and patient mean and standard deviation (s.d.) ^1H -MRS GABA+ concentration in each voxel, or GABA_A/BZR availability in each region of interest. Where these values were not reported in the published article, the authors were contacted or values were estimated from figures using a freely available ruler for Mac OS X (<http://www.pascal.com/software/freeruler/>). Where values were reported in each hemisphere separately, the mean of these values was calculated. For ^1H -MRS studies, due to partially overlapping voxel locations and to provide sufficient data for meta-analysis, data were combined into the medial frontal cortex (mFC), parietal and occipital cortices and striatum. All the variables were extracted independently by two authors (AE and DF) and cross-checked for accuracy.

Meta-analysis

Inclusion in the meta-analyses required availability of data in a given brain region from five or more studies.⁴⁷ Where there were insufficient data for meta-analysis, the findings were summarized. Where articles included more than one patient or control group, these groups were entered separately in the analyses. For each variable, the effect size statistic Hedges' *g* was calculated. Hedges' *g* is the Cohen's effect size incorporating a correction for bias from small sample sizes.⁴⁸

The meta-analysis for each variable was performed using STATA/IC, version 14, using the METAN command (StataCorp LP, College Station, TX, USA). A random-effects inverse-weighted variance model⁴⁹ was used to calculate the pooled effect size to adjust for study heterogeneity. Significance was assessed using two-sided 95% confidence intervals.

Heterogeneity was measured using the I^2 value, which indicates the percentage variance due to heterogeneity between studies compared with chance.⁵⁰ Where I^2 values indicated substantial heterogeneity ($I^2 > 50\%$), potential sources of heterogeneity were investigated by using sensitivity analysis to assess potential influences of single studies, and Egger's test⁵¹ to investigate potential publication bias.

Moderator analyses

Potential influences of study characteristics were investigated using moderator analyses. Subgroup analyses investigated the following dichotomous characteristics of data sets: (1) clinical category of subjects (first episode psychosis or schizophrenia patients versus clinical risk or genetic risk groups); (2) explicitly stated absence of GABAergic (benzodiazepine or anticonvulsant) medication at the time of scanning; (3) presence (in $>90\%$ of the sample) or absence (in 100% of the sample) of antipsychotic medication at the time of imaging. For mFC GABA ^1H -MRS studies, subgroup analyses additionally investigated potential influences of mFC voxel location (Figure 1).

Meta-regressions were conducted to explore potential influences of continuous variables relating to patient characteristics (age, percentage male in sample, illness duration, Positive and Negative Syndrome Scale total score), voxel grey matter content and publication year on GABA measures. Symptoms rated using the BPRS were converted to Positive and Negative Syndrome Scale scores using the established conversion scale of Leucht *et al.*⁵² Meta-regression analyses were performed in STATA/IC version 14 using the METAREG command, with Hedges' *g* as the outcome variable. To reduce the likelihood of chance findings, both subgroup analyses and meta-regressions required a minimum of five data sets. In all cases, the threshold for statistical significance was $P < 0.05$.

Study quality and methodological characteristics

The methodological characteristics of ^1H -MRS and PET/SPECT studies are summarized in Supplementary Tables 1 and 2, respectively. Although there are no established criteria for formal quality assessment of ^1H -MRS and PET/SPECT studies, key factors that may impact on data quality are discussed in the Supplementary Information.

RESULTS

^1H -MRS studies

Nineteen articles describing ^1H -MRS studies of GABA+ in schizophrenia were identified (Supplementary Figure 1). Of these, the article by Chen *et al.*⁵³ was excluded due to partial overlap with the larger sample reported in Kegeles *et al.*⁴⁰ Similarly, the article by Rowland *et al.*⁵⁴ was excluded due to overlap with the larger sample reported in Rowland *et al.*⁴³ Data from a single study were reported across two articles^{55,56} from which data extraction was combined. The clinical characteristics of the ^1H -MRS samples are provided in Table 1. Data used to calculate effect sizes are available in Supplementary Table 1. The methodological characteristics are provided in Supplementary Table 2.

Medial frontal cortex

Twelve articles^{38,40–43,55,57–62} involved 17 data sets for GABA+ in the mFC, providing data from a total of 409 patients and 495 controls. Meta-analysis returned a summary effect size of $g = -0.3$, which was nonsignificant (95% confidence interval: -0.6 to 0.1),

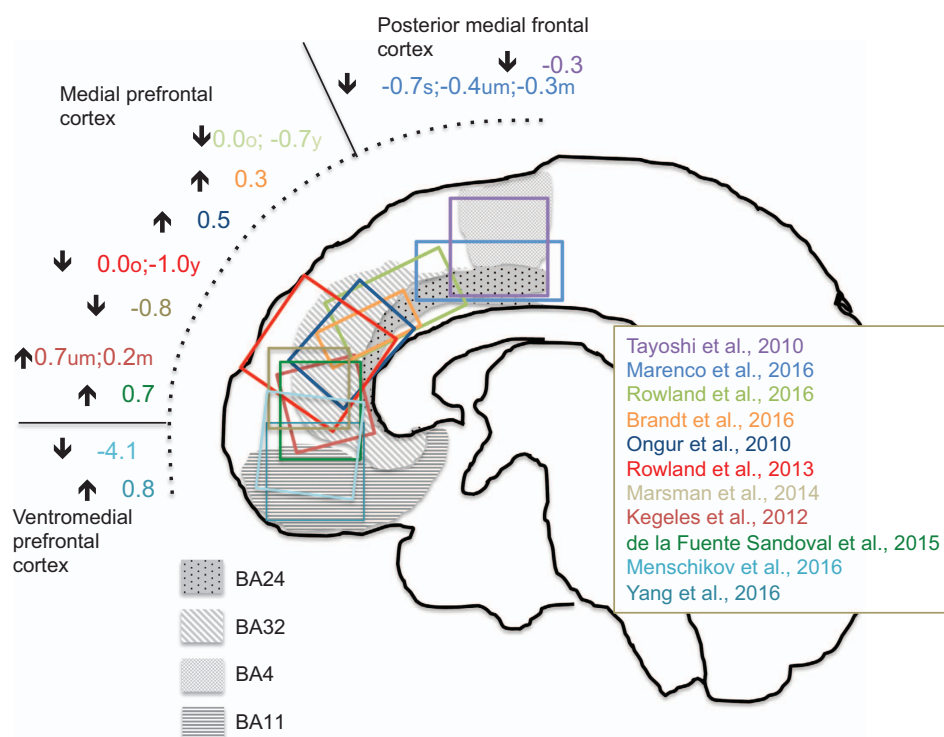


Figure 1. Voxel locations in medial frontal cortex GABA ^1H -MRS studies. Numbers provide effect sizes (Hedge's g) for the difference in ^1H -MRS GABA level between patients and control participants for each study. Negative effect sizes indicate lower GABA in patients; positive effect sizes indicate lower GABA in controls. Subgroup membership was defined by voxel locations primarily in the Brodmann Areas (BA) BA4 and BA24 (posterior medial frontal cortex), BA24 and BA32 (medial prefrontal cortex) or BA24 and BA11 (ventromedial prefrontal cortex). ^1H -MRS, proton magnetic resonance spectroscopy.

$P=0.1$, Figure 2a). The I^2 value was 84%, indicating a significant ($P<0.001$) and considerable heterogeneity across data sets.⁵⁰ Visual inspection of the Forrest plot (Figure 2a) shows that one study⁶¹ was clearly an outlier, and that of the remaining studies, approximately half reported higher GABA+ levels in patients than controls, while the other half reported the opposite. The recalculated summary effect size after removal of the outlying data set was $g=-0.1$, which was also nonsignificant (95% confidence interval: -0.4 to 0.2 , $P=0.5$, $I^2=69\%$). Sensitivity analyses did not return significant results on any iteration, and the Eggers test did not suggest publication bias.

Available data sets permitted a series of subgroup analyses, which involved studies that (i) only included patients with a first episode of psychosis or schizophrenia (14 data sets^{38,40,42,43,55,57–60,62}); (ii) explicitly excluded patients taking benzodiazepine or anticonvulsant medication (eight data sets^{38,41–43}); (iii) included patients of whom $>90\%$ were being treated with antipsychotic medication (12 data sets^{38,40,42,43,55,57,58,60}); (iv) excluded subjects who had taken antipsychotic medication (five data sets^{38,40,41,62}); or (v) included only ^1H -MRS voxels in the medial prefrontal area of the medial frontal cortex (Figure 1; 10 data sets^{40–43,57,59,60}). All of these subgroup analyses returned nonsignificant summary effect sizes and I^2 values $>50\%$. Meta-regression did not reveal any significant relationships between mFC GABA+ and age, illness duration, symptom severity, percentage grey matter in the voxel or publication date. There was a significant association with percentage of males in the sample (17 observations, $\beta=-0.04$; $t=-2.5$; $P=0.03$), but this was driven by outlying values from one study that included only male subjects.⁶¹ The effect was no longer significant when this study had been removed ($\beta=-0.004$; $t=-0.4$; $P=0.7$).

Parietal/occipital cortex

Meta-analysis of GABA+ in the parietal/occipital cortex included seven observations across six articles,^{39,55,57,59,63,64} providing data from a total of 139 patients and 111 controls. The summary effect size was nonsignificant ($g=-0.3$; 95% confidence interval: -0.9 to 0.3 , $P=0.3$, $I^2=80\%$; Figure 2b) with no indication of publication bias. Limiting the analysis to observations in first episode psychosis or schizophrenia (six observations^{39,55,57,59,63,64}) also returned nonsignificant summary effect sizes. There were insufficient data to investigate further subgroups. All meta-regression analyses were nonsignificant.

Striatum

Five data sets reported GABA+ in the striatum across four articles.^{39,41,55,58} The summary effect size was not significant (123 patients, 95 controls, $g=-0.004$; 95% confidence interval: -0.7 to 0.7 , $P<1.0$, $I^2=82\%$ Figure 2c), with no indication of publication bias. There were insufficient data for subgroup analyses and meta-regression returned nonsignificant findings.

Other brain regions

One study⁴⁰ examined GABA+ in the dorsolateral prefrontal cortex, one⁴² examined GABA in the centrum semiovale and one⁶⁵ examined GABA+ in the left hippocampus (Table 1, Figure 2d). There were insufficient data for meta-analysis and no significant group differences in GABA+ were reported for these brain regions.

GABA_A/BZR availability

Ten articles were initially identified, which reported GABA_A/BZR availability in schizophrenia.^{66–75} Of these, three were excluded: one because it was a conference abstract rather than a paper,⁶⁶

Table 1. ¹H-MRS GABA data sets: clinical characteristics of the samples

| Region | First author (reference) | Year | Patient group | g | Sample size | | SCZ %M | SCZ age mean | %AP | %BZ | PANSS | DOI |
|-------------|-------------------------------------|------|---------------|------|-------------|-----|--------|--------------|------|-----|-------|------|
| | | | | | C | SCZ | | | | | | |
| mFC | Goto ^{55,56} | 2009 | FEP | -0.2 | 18 | 18 | 50 | 29 | 100 | NR | 68 | 0.5 |
| | Öngür ⁵⁷ | 2010 | SCZ | 0.5 | 19 | 21 | 67 | 39 | 95 | 76 | 51 | 21 |
| | Tayoshi ⁵⁸ | 2010 | SCZ | -0.3 | 29 | 38 | 53 | 34 | 100 | 42 | 51 | 21 |
| | Kegeles ⁴⁰ | 2012 | SCZ unmed | 0.7 | 11 | 16 | 69 | 32 | 0 | 19 | 71 | 7 |
| | Kegeles ⁴⁰ | 2012 | SCZ med | 0.2 | 11 | 16 | 69 | 32 | 100 | 19 | 57 | 9 |
| | Rowland ⁴² | 2013 | SCZ young | 0.0 | 10 | 11 | 82 | 30 | 100 | 0 | 63 | 7.7 |
| | Rowland ⁴² | 2013 | SCZ old | -1.0 | 10 | 10 | 70 | 51 | 100 | 0 | 57 | 25.5 |
| | Marsman ⁵⁹ | 2014 | SCZ | -0.8 | 19 | 13 | 76 | 28 | 100 | 35 | 53 | 6.5 |
| | De la Fuente Sandoval ⁴¹ | 2015 | CHR | 0.7 | 24 | 23 | 65 | 21 | 0 | 0 | NR | — |
| | Brandt ⁶⁰ | 2016 | SCZ | 0.3 | 24 | 24 | 79 | 38 | 100 | 17 | NR | NR |
| | Marenco ³⁸ | 2016 | Siblings | -0.7 | 61.3 | 31 | 55 | 30 | 0 | 0 | NR | — |
| | Marenco ³⁸ | 2016 | SCZ unmed | -0.4 | 61.3 | 25 | 72 | 28 | 0 | 0 | NR | 6.0 |
| | Marenco ³⁸ | 2016 | SCZ med | -0.3 | 61.3 | 70 | 71 | 31 | 100 | 36 | NR | 9.5 |
| | Menschikov ⁶¹ | 2016 | CHR | -4.1 | 26 | 21 | 100 | NR | NR | NR | NR | — |
| | Rowland ⁴³ | 2016 | SCZ young | 0.0 | 40 | 29 | 69 | 26 | 93 | 0 | NR | 5.6 |
| | Rowland ⁴³ | 2016 | SCZ old | -0.7 | 37 | 31 | 61 | 48 | 90 | 0 | NR | 24 |
| | Yang ⁶² | 2016 | FEP | 0.8 | 23 | 22 | 41 | 26 | 0 | NR | 69 | 1.6 |
| POC | Goto ^{55,56} | 2009 | FEP | 0.2 | 18 | 18 | 50 | 29 | 100 | NR | 68 | 0.5 |
| | Öngür ⁵⁷ | 2010 | SCZ | 0.4 | 19 | 21 | 67 | 39 | 95 | 76 | 51 | 21 |
| | Yoon ⁶³ | 2010 | FEP/SCZ | -2.6 | 13 | 13 | 85 | 28 | 62 | NR | 73 | NR |
| | Kelemen ⁶⁴ | 2013 | FEP | -0.7 | 20 | 28 | 64 | 25 | 0 | 0 | 88 | 0.8 |
| | Marsman ⁵⁹ | 2014 | SCZ | 0.3 | 19 | 15 | 76 | 28 | 100 | 35 | 53 | 6.5 |
| | Thakkar ³⁹ | 2016 | Sibling | 0.0 | 12 | 23 | 53 | 31 | 0 | 0 | NR | — |
| | Thakkar ³⁹ | 2016 | SCZ | -0.5 | 12 | 21 | 71 | 36 | 100 | 24 | 49 | 14 |
| Striatum | Goto ^{55,56} | 2009 | FEP | -0.8 | 18 | 18 | 50 | 29 | 100 | NR | 68 | 0.5 |
| | Tayoshi ⁵⁸ | 2010 | SCZ | -0.2 | 29 | 38 | 53 | 34 | 100 | 42 | 51 | 21 |
| | De la Fuente Sandoval ⁴¹ | 2015 | CHR | 1.3 | 24 | 23 | 65 | 21 | 0 | 0 | NR | — |
| | Thakkar ³⁹ | 2016 | Sibling | -0.3 | 12 | 23 | 53 | 31 | 0 | 0 | NR | — |
| | Thakkar ³⁹ | 2016 | SCZ | -0.1 | 12 | 21 | 71 | 36 | 100 | 24 | 49 | 14 |
| dIPFC | Kegeles ⁴⁰ | 2012 | SCZ unmed | -0.1 | 11 | 16 | 69 | 32 | 0 | 19 | 71 | 7 |
| dIPFC | Kegeles ⁴⁰ | 2012 | SCZ med | -0.4 | 11 | 16 | 69 | 32 | 100 | 19 | 57 | 9 |
| Hippocampus | Stan ⁶⁵ | 2015 | SCZ | -0.2 | 16 | 18 | 78 | 42 | 61 | 28 | NR | NR |
| CSO | Rowland ⁴² | 2013 | SCZ younger | 0.2 | 10 | 11 | 82 | 30 | 100 | 0 | 63 | 7.7 |
| CSO | Rowland ⁴² | 2013 | SCZ older | -0.7 | 10 | 10 | 70 | 51 | 1000 | 0 | 57 | 25.5 |

Abbreviations: %AP, percentage of SCZ group currently taking antipsychotic medication; %BZ, percentage of SCZ group currently taking benzodiazepine or anticonvulsant medication; C, control; CHR, clinical high risk; CSO, centrum semiovale; dIPFC, dorsolateral prefrontal cortex; DOI, mean duration of illness in years; FEP, first episode psychosis; g, Hedge's *g* effect size; %M, percentage of male in the SCZ sample; mFC, medial frontal cortex area; NR, not reported; PANSS, Positive and Negative Syndrome Scale mean total symptom score; POC, parietal/occipital cortex; SCZ, schizophrenia or schizophreniform disorder; sibling, healthy siblings of patients with SCZ. Age is expressed in years (mean).

one because it presented previously published data⁶⁹ and one because it did not include a control group⁶⁸ (Supplementary Figure 1). The clinical and methodological characteristics of the remaining seven articles^{67,70–75} are provided in Table 2 and Supplementary Table 3, respectively. There were not sufficient ROI data to permit meta-analyses in any brain region. None of the individual ROI studies detected any significant differences in regional GABA_A/BDZ receptor availability between patients and controls (Figure 3).^{67,71,72,75} Of the voxel-wise studies, one reported significantly lower GABA_A/BZR availability in clinical high-risk subjects in the right caudate nucleus,⁷³ one reported lower GABA_A/BDZ receptor availability in the left precentral gyrus in schizophrenia,⁷⁰ and one reported decreased GABA_A/BDZ receptor availability in the subgenual cingulate cortex and left temporal pole, but increased GABA_A/BDZ receptor availability in the right inferior occipital gyrus in schizophrenia.⁷⁴

Frankle *et al.*⁷⁵ compared antipsychotic-naïve and antipsychotic-exposed schizophrenia, finding elevated baseline GABA_A/BZR availability in the antipsychotic-naïve group across all brain regions

investigated. Lee *et al.*⁷⁴ compared patients with schizophrenia currently taking aripiprazole or risperidone, and detected lower GABA_A/BZR availability in the right medial, dorsolateral prefrontal, frontal polar and right premotor cortices in the aripiprazole group.

Three articles examined the relationship between GABA_A/BZR availability and symptom severity.^{70,71,75} None of these found significant associations. One article reported inverse relationships between positive symptoms and receptor binding in the medial temporal lobe, and between negative symptoms and binding in the medial frontal region.⁶⁷ Another article reported an inverse relationship between receptor binding in the prefrontal cortex and hippocampus and negative symptom severity.⁷²

Frankle *et al.*⁷⁵ also examined the change in [¹¹C] flumazenil V_T following administration of the GABA transporter inhibitor tiagabine to increase GABA levels. This study detected no difference between the overall schizophrenia group compared with controls, but a smaller tiagabine-induced change in V_T (GABA increase) in antipsychotic-naïve patients, but not in antipsychotic-exposed patients, compared with controls.⁷⁵

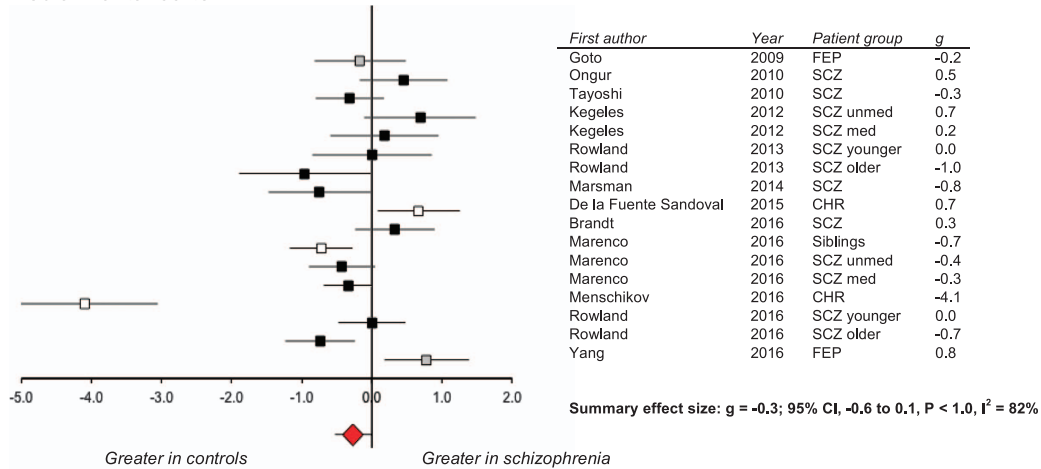
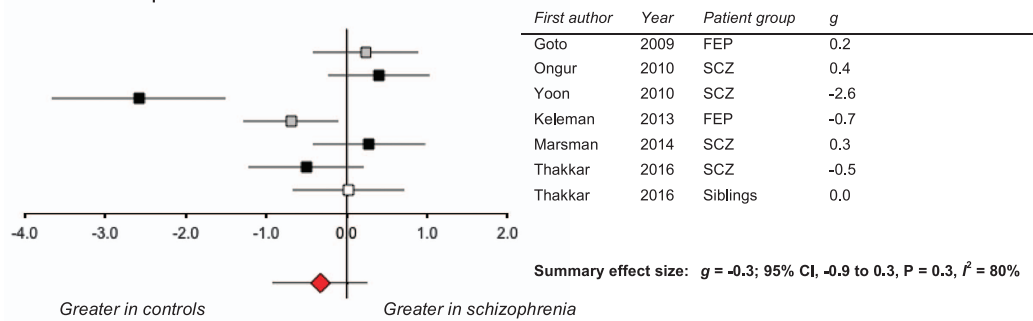
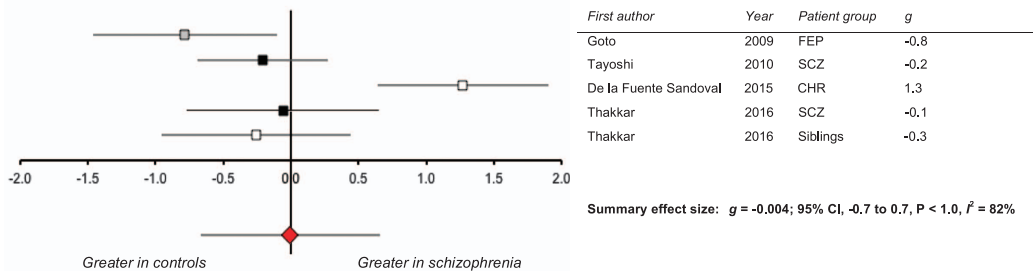
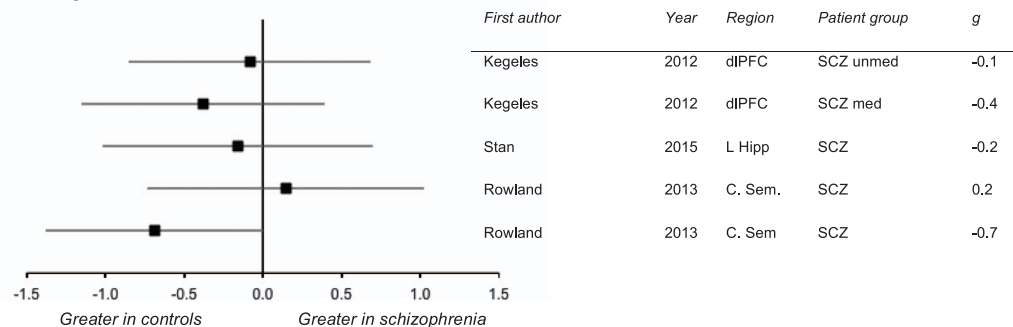
a Medial frontal cortex**b** Parietal / Occipital Cortex**c** Striatum**d** Other regions

Figure 2. (a–d) Forest plots showing effect sizes (Hedge's g) for ^1H -MRS GABA studies in schizophrenia versus control. Error bars represent 95% confidence intervals. Black squares indicate data from clinical patient samples (FEP or SCZ) while white squares indicate data from CHR or sibling samples. CHR, clinical high risk; FEP, first episode psychosis; ^1H -MRS, proton magnetic resonance spectroscopy; SCZ, schizophrenia or schizoaffective disorder; sibling, unaffected siblings of patients with schizophrenia; med, currently receiving antipsychotic medication; unmed, currently unmedicated with antipsychotics.

Table 2. PET/SPECT GABA_A/BDZ receptor availability data sets: clinical characteristics of the samples

| First author | Year | Patient group | Sample size | | SCZ %M | SCZ age mean | %AP | %BZ | PANSS | DOI |
|---------------------------|------|---------------|-------------|-----|-----------|--------------------|-----|-----|-------|-----|
| | | | C | SCZ | | | | | | |
| Busatto ⁶⁷ | 1997 | SCZ | 12 | 15 | 93 | 29 | 60 | NR | NR | 6.5 |
| Verhoeff ⁷⁰ | 1999 | SCZ | 24 | 25 | 100 | 41 | 80 | 0 | NR | NR |
| Abi-Dargham ⁷¹ | 1999 | SCZ | 16 | 16 | 100 | 44 | 69 | 0 | NR | NR |
| Asai ⁷² | 2008 | SCZ | 11 | 12 | 55 | 33 | 0 | 0 | 90.4 | NR |
| Lee ⁷⁴ | 2013 | SCZ | 18 | 17 | 47 | 29 | 100 | 0 | 60.5 | 4.1 |
| Kang ⁷³ | 2014 | CHR | 15 | 11 | 66 | 19 | 18 | 0 | NR | — |
| Frankle ⁷⁵ | 2015 | SCZ | 22 | 17 | 65 | 28 | 0 | NR | 83 | NR |

Abbreviations: %AP, percentage of SCZ group currently taking antipsychotic medication; %BZ, percentage of SCZ group currently taking benzodiazepine or anticonvulsant medication; C, control; CHR, clinical high risk; DOI, mean duration of illness in years; %M, percentage of male in SCZ sample; NR, not reported; PANSS, Positive and Negative Syndrome Scale mean total symptom score; SCZ, schizophrenia. Age is expressed in years, mean; regional effect sizes are provided in Figure 2.

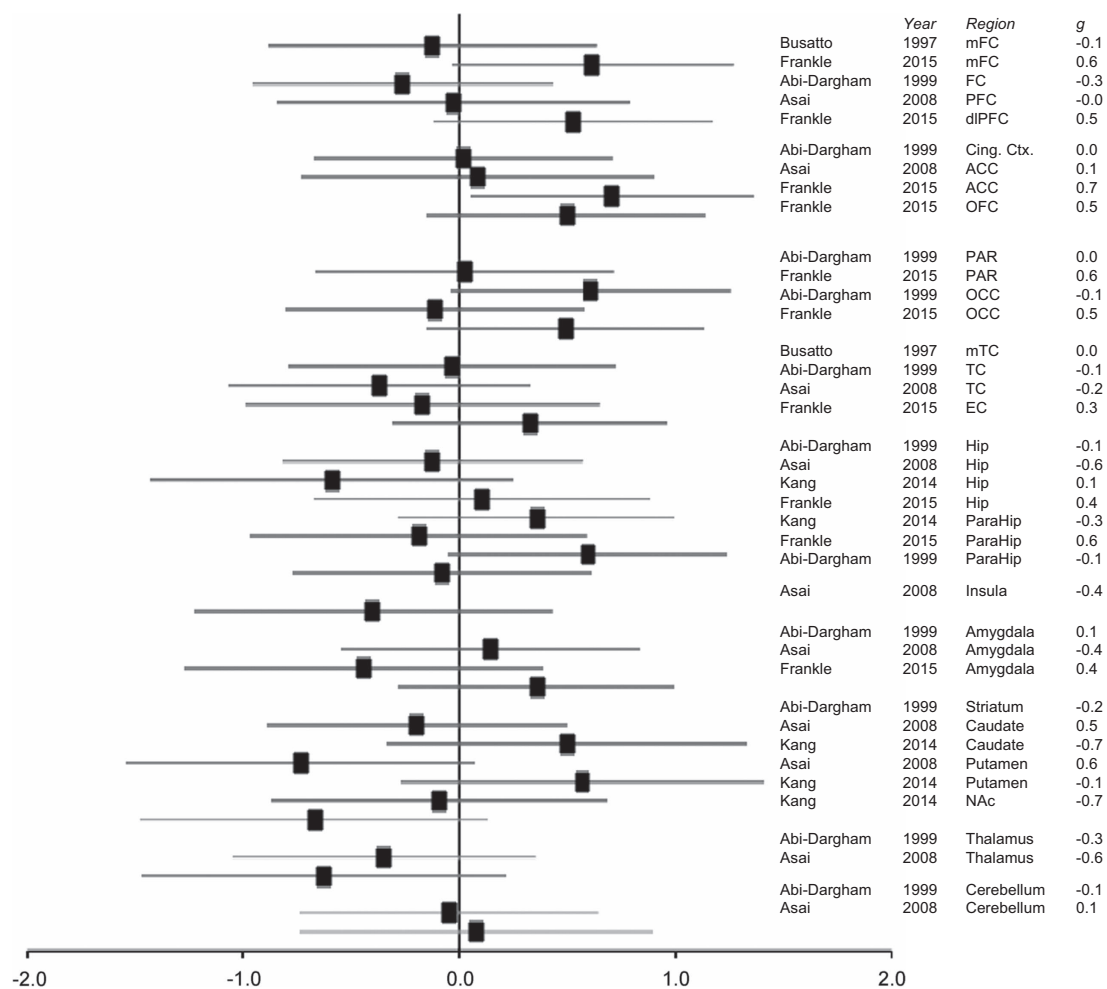


Figure 3. Illustration of effect sizes (Hedge's *g*) for PET/SPECT studies of regional GABA_A/BDZ receptor availability in schizophrenia versus control. Error bars represent 95% confidence intervals. ACC, anterior cingulate cortex; Cing. Ctx, cingulate cortex; dIPFC, dorsolateral prefrontal cortex; EC, entorhinal cortex; FC, frontal cortex; Hip, hippocampus; ¹H-MRS, proton magnetic resonance spectroscopy; mFC, medial frontal cortex; mTC, medial temporal cortex; NAc, nucleus accumbens; OFC, orbitofrontal cortex; ParaHip, parahippocampus; PFC, prefrontal cortex; TC, temporal cortex. Studies reporting only voxel-wise analyses^{70,74} are excluded from the figure.

DISCUSSION

The main finding of this article is that meta-analyses of ¹H-MRS studies found no evidence for significantly altered GABA+ concentrations in patients with schizophrenia compared with healthy volunteers in the medial frontal cortex, parieto-occipital

cortex or striatum. Analyses revealed a substantial level of heterogeneity across studies, which may relate to differences in patient samples and ¹H-MRS methodological characteristics. Although there were insufficient studies of GABA_A/BZR availability to perform meta-analysis, a systematic review of these studies

found no consistent evidence for altered GABA_A/BZR availability in schizophrenia.

To our knowledge, this is the first meta-analysis of ¹H-MRS GABA studies in schizophrenia. Postmortem studies in schizophrenia find reductions in GAD67,^{1–3} which is responsible for the majority of basal GABA synthesis in the cortex.⁶ The ¹H-MRS GABA signal may reflect the entire GABA content of the voxel (that is, intracellular and extracellular, and involved in metabolism or neurotransmission). Recent work argues that the ¹H-MRS GABA signal predominantly relates to extracellular, extra-synaptic GABA providing tonic inhibitory tone, rather than GABA involved in phasic synaptic neurotransmission.^{76,77} Theoretically, the ¹H-MRS GABA signal should therefore be sensitive to GAD67 reduction. However, our meta-analysis of *in vivo* ¹H-MRS GABA studies in schizophrenia found that, although in cortical regions the summary effect sizes were consistent with lower GABA levels, these effect sizes were small and nonsignificant.

An absence of large, detectable differences in GABA concentrations in schizophrenia *in vivo* could reflect normalization by compensatory mechanisms at the cellular or network level,¹⁵ and it is unknown whether GAD67 reduction in schizophrenia is primary, or secondary to other pathological mechanisms such as glutamatergic dysfunction.^{78,79} Furthermore, one limitation of ¹H-MRS is that it measures total GABA concentrations within a relatively large voxel (mean 30 ml in the studies included in this article), which is determined *a priori*, and cannot discriminate between GABA levels in different cell types. This limits the application of ¹H-MRS in addressing the cell- and network- specific GABA abnormalities hypothesized to occur in schizophrenia.¹⁵

The ¹H-MRS meta-analysis also reflects several limitations in the currently available literature. Sixteen studies contributed to the meta-analysis, but there were relatively few investigations in each brain region, with non-overlapping voxel placements (for example in the mFC), variability between clinical samples and ¹H-MRS methodological approaches and high heterogeneity. Meta-analysis revealed substantial variability in the findings across studies. For example, there were approximately equal numbers of studies reporting increases of GABA+ in the medial frontal cortex in schizophrenia as there were studies reporting reductions (Figure 2a), and all meta-analyses were associated with significant and high levels of heterogeneity. This may reflect between-study differences in patient samples, methodological approaches or relate to inconsistency in ¹H-MRS GABA measurement. Regional brain GABA levels in schizophrenia may vary with the stage of the disorder, as has been reported in some individual studies,^{38,40,42,43} and appears to be evident for brain glutamate levels.⁸⁰ Our analysis was limited in that there were too few studies to perform meta-analyses of all patient subgroups in all regions. However, exclusion of data sets from 'at risk' participants (and thus restricting the analysis to patients with schizophrenia) did not change our findings. Similarly, the findings in the mFC remained nonsignificant and heterogeneous when the analysis was limited to either antipsychotic unmedicated or treated patients, or restricted to the prefrontal part of the medial frontal region. Moreover, meta-regression found no effect of duration of illness, participant age or symptom severity on GABA effect sizes. Nevertheless, there are several other clinical and methodological variables that might contribute to heterogeneity, such as the duration of treatment, time off medication or substance use, which we were not able to investigate in this meta-analysis. It is also possible that more complex relationships exist between two or more study variables on the GABA effect size, for example the location of GABA dysfunction within the mFC may vary with age or illness stage.

Owing to limited data availability, our meta-analysis did not account for the several methodological differences between studies that may have impacted on data quality. Differences in field strength, voxel size and acquisition times will translate to large between-study differences in the signal to noise ratio, and it

was not possible to evaluate spectral quality in 7 of the 16 included articles (see Supplementary Information). Only two recent studies included methodology to isolate the GABA signal from macromolecule contamination,^{39,43} which is a key area for future methodological development. Therefore, while the meta-analyses did not indicate differences in regional GABA levels between patients and controls, this interpretation is limited pending publication of further individual studies. Future studies should directly compare different patient samples, maximize signal to noise ratio, address macromolecule contamination and include detailed and transparent reporting of spectral quality. On the basis of postmortem evidence, we suggest that key regions for investigation include the dorsolateral prefrontal cortex, anterior cingulate cortex and hippocampus.^{3,10,17,81–83}

Our systematic review of PET/SPECT studies examining GABA_A/BZR availability also suggested an overall lack of evidence for differences in patients compared with controls, with no significant regional group differences in four out of seven studies.^{67,71,72,75} However, the three voxel-wise studies all reported lower GABA_A/BZR availability in patients compared with controls, but there was no consistency across studies in the regions where these differences were detected.^{70,73,74} All identified studies applied PET/SPECT radiotracers with affinity at the BZ site of the GABA_A/BZR complex, and postmortem autoradiography studies of availability of BZ binding sites have also produced inconsistent results.^{22–27} This contrasts with reports of increases in availability of the GABA binding site on the GABA_A/BZR in schizophrenia postmortem,^{16–22} for which *in vivo* radiotracers are currently unavailable. A further consideration is that several PET/SPECT studies estimated regional GABA_A/BZR availability relative to white matter,^{67,72–74} which may be confounded by the presence of white matter abnormalities in schizophrenia (see ref. 84).

In contrast to ¹H-MRS, GABA_A/BZR PET imaging may be able to measure changes in synaptic GABA concentrations. Frankle *et al.*⁷⁵ used this approach to examine the increase in GABA following administration of the presynaptic GABA reuptake inhibitor tiagabine. Although they found no difference between patients with schizophrenia and controls, when the analysis was restricted to the subgroup of patients that were antipsychotic-naïve, the increase in GABA following tiagabine was significantly diminished. Tiagabine-induced increases in cortical GABA are not detectable using ¹H-MRS,^{85,86} which is consistent with the view that the GABA ¹H-MRS signal principally reflects nonsynaptic GABA. Pharmacologically induced alterations in synaptic GABA may be more sensitively imaged with [¹¹C]Ro15-4513 PET, because it is a GABA_A/BZR inverse agonist with greater selectivity for intra-synaptic receptors.⁸⁷ In the future, combination of this approach with ¹H-MRS in the same subjects, and potentially during the same scanning session on combined PET-MR platforms, might investigate dysfunction of synaptic versus nonsynaptic GABA in schizophrenia.

Cluster analyses of postmortem data find that GABAergic deficits are not present in all schizophrenia patients, but characterize a patient subgroup of approximately 50% of the postmortem sample.^{88,89} This postmortem 'Low GABA Marker' (LGM) phenotype⁸⁹ does not readily relate to illness severity, psychoactive medication or substance use at the time of death.^{88,89} If a LGM subgroup could similarly be identified using *in vivo* biomarkers, this might lead to a stratified approach to treatments that address GABAergic dysfunction. It is possible that the heterogeneity in ¹H-MRS studies may also reflect GABAergic subgroups of patients, either within- or between-study samples, which are again not readily identifiable by clinical variables. However, unlike postmortem studies, GABA imaging studies did not show consistently higher variability in GABA measurements in the patient compared with the control group (Supplementary Table 2). Combination of GABA ¹H-MRS or GABA PET/SPECT with electroencephalogram gamma-band oscillations in schizophrenia,^{53,75,90} which reflect on parvalbumin neuron

activity,⁹¹ may help determine whether such GABAergic subgroups of patients are identifiable *in vivo*.

In conclusion, at present, the neuroimaging literature suggests that brain GABA function, as indexed by ¹H-MRS GABA concentrations and GABA_A/BZB site availability, does not provide a consistent pattern of alteration in schizophrenia. However, the total number of studies completed in this field is still relatively small, and most studies to date have involved small patient samples (typically 15–30 patients), and varying data quality (see Supplementary Information for discussion). It remains unclear if the absence of overall differences reflects confounding effects of age, stage of illness, medications or other unknown factors. Further studies using larger and more homogeneous samples may therefore be useful, as would studies directly comparing specific patient subgroups. Advances in both ¹H-MRS and PET methodologies may reveal specific aspects of GABA dysfunction *in vivo* in schizophrenia within the next few years.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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